CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 65-017

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-017 APPLICANT: Eon Labs Manufacturing, Inc.

DRUG PRODUCT: Cyclosporine Capsules, 100 mg and 25 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 500 mL of 0.1N HCl containing 2 mg/mL of Lauryldimethylamine-N-Oxide at 37°C using USP 23 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

> Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

File (4)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 65-017 SPONSOR : Eon Labs Manufacturing, Inc.

DRUG AND DOSAGE FORM : Cyclosporine Capsules

STRENGTH(S) : 25 mg

TYPES OF STUDIES : N/A

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY : N/A

DISSOLUTION : Dissolution testing for the 25 mg strength is acceptable. A waiver is granted for the 25 mg strength.

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
other _____		

PRIMARY REVIEWER : Moheb H. Makary BRANCH : III

INITIAL : ___ /S/ _____ DATE : 5-10-99

TEAM LEADER : Barbara M. Davit BRANCH : Branch III

INITIAL : _ /S/ _____ DATE : 5/10/99

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : ___ _____ DATE : 5/26/99

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-017 APPLICANT: Eon Labs Manufacturing, Inc.

DRUG PRODUCT: Cyclosporine Capsules, 100 mg and 25 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 500 mL of 0.1N HCl containing 2 mg/mL of Lauryldimethylamine-N-Oxide at 37°C using USP 23 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

> Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #65-017

/S/

BIOEQUIVALENCY - ACCEPTABLE submission date: March 30, 1999

✓ AMS 1. **STUDY AMENDMENT** (STA) Strengths: 25 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

Cyclosporine
100 mg Soft Gelatin Capsules
AADA #65-017
Reviewer: Moheb H. Makary
W 65017dw.399

Eon Labs Manufacturing, Inc.
Laurelton, New York
Submission Date:
March 30, 1999

REVIEW OF AN AMENDMENT

I. Objective:

The firm has submitted this amendment to provide for the addition of 25 mg Capsules as a product line extension to its ANDA for Cyclosporine Capsules, 100 mg (submission dated June 8, 1998). The firm is requesting a waiver of *in vivo* study requirements under 21 CFR 320.22 (d)(2).

In support of the waiver request the firm has submitted comparative formulation data for the 100 mg and 25 mg capsules and comparative *in vitro* dissolution testing between the firm's 25 mg capsules vs Neoral^{R} 25 mg capsules.

II. Formulations:

Eon's formulations for its Cyclosporine Soft Gelatin Capsules, 100 mg and 25 mg are shown below:

Component	100 mg mg/Capsule	25 mg mg/Capsule
Cyclosporine,	100.0	25.0
alcohol,		
d-a Tocopheryl polyethylene glycol 1000 succinate		
Polyethylene glycol		
Polyoxyl 40 hydrogenated Castor oil NF		

Capsule Shell

Component	
Purified water,	
Gelatin,	
Sorbitol	
),	)
Total	

III. In Vitro Dissolution Testing: (Pharmacopeial Forum, May-June 1998, Volume 24, Number 3, page 6155, method A)

The firm has submitted dissolution results for its Cyclosporine, 25 mg Soft Gelatin Capsules. The results are shown in Table I.

The dissolution testing for the test and reference products is summarized below:

Method:	USP apparatus II at 75 rpm
Medium:	500 mL of 0.1N HCl containing 2 mg/mL
of	Lauryldimethylamine-N-Oxide
Number of Capsules:	12
Test product:	Eon's Cyclosporine Capsules, 25 mg, lot #801218
Reference product:	Novartis' Neoral^{R} Capsules, 25 mg, lot #23398

Specification:

IV. Comments:

1. The firm has established the bioequivalency of the 100 mg capsules in fasting and food studies submitted in its original application on June 8, 1998.

2. The formulation for cyclosporine 25 mg capsules is proportionally similar to the 100 mg capsules.

3. The *in vitro* dissolution testing submitted by the firm on its cyclosporine capsules, 25 mg, is acceptable. It should be noted that the test 25 mg capsules vs the test 100 mg capsules and the test 25 mg capsules vs the reference 25 mg capsules meet the F2 criteria (Table I).

4. The waiver may be granted based on 21 CFR 320.22(d)(2).

IV. Recommendations:

1. The dissolution testing conducted by the firm on its Cyclosporine Capsules, 25 mg, lot #801218, is acceptable. The formulation for the 25 mg strength is proportionally similar to the 100 mg strength of the test product which underwent acceptable bioequivalence testing.

2. A waiver of *in vivo* bioequivalence study requirements for the 25 mg capsule is granted. The Division of Bioequivalence deems Cyclosporine Capsules, 25 mg, manufactured by Eon Labs Manufacturing, Inc., to be bioequivalent to Neoral[R] Capsules, 25 mg, manufactured by Novartis.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of 0.1N HCl containing 2 mg/mL of Lauryldimethylamine-N-Oxide at 37°C using USP 23 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

> Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

The firm should be informed of the above recommendations.

/S/
Moheb H. Makary, Ph.D. Date: 5/10/99
Review Branch III
Division of Bioequivalence

RD INITIALLED BDAVIT /S/
FT INITIALLED BDAVIT Date: 5/10/99

/S/
Concur: _____ Date: 5/26/99
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Table I. In Vitro Dissolution Testing

Drug (Generic Name): Cyclosporine 25 mg Soft Gelatin Capsule
Dose Strength: 25 mg
ANDA No.: 65-017
Firm: Eon Labs Manufacturing, Inc.
Submission Date: March 30, 1999
File Name: 65017sd.399

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 75
No. Units Tested: 12
Medium: 500 mL of 0.1N HCl containing 2 mg/mL of Lauryldimethylamine-N-Oxide
Specifications: NLT (Q) in 60 minutes
Reference Drug: Neoral®
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #801218 Strength(mg) 25			Reference Product Lot #23398 Strength(mg) 25		
	Mean %	Range	%CV	Mean %	Range	%CV
15	90.5		6.8	78.9		11.0
30	97.8		0.5	91.6		3.7
45	98.9		0.5	96.6		1.7
60	98.8		0.5	99.0		1.4
60	99.2		1.0	100.2		1.1

Date
USER MHM
n = 5

F2 = 60.83

ANDA # 65-017

[redacted]

	25 mg Test	25 mg Ref	(R-T)2
	90.5	78.9	134.56
	97.8	91.6	38.44
	98.9	96.6	5.29
	98.8	99	0.04
	99.2	100.2	1.00

Date

USER MHM

n = 5

F2 = 73.87

ANDA # 65-017

[redacted]

25 mg Test	100 mg Test	(R-T)2
90.5	97.5	49.00
97.8	97.8	0.00
98.9	98.3	0.36
98.8	98.1	0.49
99.2	98.4	0.64

Cyclosporine
100 mg Soft Gelatin Capsules
AADA #65-017
Reviewer: Moheb H. Makary
WP 65017sd.698

Eon Labs Manufacturing, Inc.
Laurelton, New York
Submission Date:
June 8, 1998
September 11, 1998
November 12, 1998

Review of In-Vivo Bioequivalence Studies

I. Objective:

The firm submitted two bioequivalence studies to assess the bioequivalence of Eon's Cyclosporine Soft Gelatin Capsules, 100 mg, to Novartis' Neoral^{R} 100 mg Capsule (microemulsion). Disintegration testing for Eon's Cyclosporine 100 mg capsules and Neoral^{R} 100 mg capsules and the composition for the Cyclosporine 100 mg capsules were also submitted.

II. BACKGROUND:

Cyclosporine (cyclosporin A) is a potent immunosuppressive antibiotic indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. It is also indicated for treatment of chronic rejection in patients previously treated with other immunosuppressive agents. The immunosuppressive action of cyclosporine appears mainly to involve inhibition of lymphocytic proliferation and function.

Following oral administration, absorption of cyclosporine from the gastrointestinal tract is variable and incomplete. The time to peak blood cyclosporine concentrations (Tmax) ranged from 1.5 to 2.0 hours in renal transplant patients. The administration of food with cyclosporine decreased the area under the curve (AUC) and peak drug blood concentration (Cmax). A high-fat meal consumed 30 minutes before cyclosporine administration decreased the AUC by 13% and the Cmax by 33%. The effects of a low-fat meal were similar.

Cyclosporine is distributed largely outside the blood volume. In blood, the distribution is concentration-dependent, with approximately 33-47% in plasma, 4-9% in lymphocytes, 5-12% in granulocytes, and 41-58% in erythrocytes. At high concentrations, the binding capacity of leukocytes and erythrocytes becomes saturated. In plasma, approximately 90% is bound to proteins, primarily lipoproteins.

The disposition of cyclosporine from blood is generally biphasic, with a terminal half-life of approximately 8.4 hours (range 5 to 18 hours). Elimination is primarily biliary with only 6% of the dose (parent drug and metabolites) excreted in the urine. Cyclosporine is extensively metabolized but there is no major metabolic pathway. The role of metabolites in immunosuppression has not been established.

Cyclosporine capsules products are marketed by Novartis as Sandimmune® capsules, 25, 50 and 100 mg and Neoral® soft gelatin capsules (cyclosporine capsules for microemulsion), 25, 50 and 100 mg. Because the bioavailability of Neoral® is greater than that of Sandimmune®, the products are not bioequivalent and cannot be used interchangeably without physician supervision.

III. Study #ANA-97-132 for Single-Dose, two-way Crossover Study of Cyclosporine Capsule, 100 mg, Under Fasting Conditions

The objective of this study was to compare the rate and extent of absorption of a test and a reference cyclosporine 100 mg soft gelatin capsule (test cyclosporine 100 mg soft gelatin capsule versus Sandoz Pharmaceuticals Corporation USA (New name Novartis) Neoral®) administered as 2 x 100 mg soft gelatin capsules.

Sponsor: Eon Labs Manufacturing, Inc.
Laurelton, New York

Study site:

Study design: Open-label, single-dose, fasted, randomized, two-period crossover.

Dosing date: The study was conducted in two groups.
Group 1(subject Nos. 1-32, except 20),
Period I December 15, 1997
Period II January 4, 1998
Group II (subject Nos. 20, 33-38)
Period I January 4, 1998
Period II January 18, 1998

Analytical Date: Samples were analyzed from January 22 to March 13, 1998.

Subjects eligibility: A total of 38 healthy non-smoking, Caucasian males were enrolled and 35 subjects completed the study. All subjects met the inclusion and exclusion

criteria described in the protocol and were judged to be medically healthy based on medical history, medication history, physical examination, ECG, urine drug screen, urinalysis and clinical laboratory tests, including HIV antibody, hepatitis B (HB_sAg) and C (HCV). Their ages ranged from 18 to 43 and their weights did not deviate by more than 15% from their ideal body weights, based on the 1983 Metropolitan height and weight tables. Screening procedures took place within 28 days prior to Period 1.

The study was conducted in two groups. Period 1 of ANA-97-132 (Subject Nos. 01-32, except 20) began on December 21, 1997 while Period 1 of ANA-97-132 (Subject Nos. 20, 33-38) began on January 04, 1998.

Restrictions: Subjects were instructed to abstain from food or drinks containing caffeine and/or xanthine (i.e. coffee, tea, caffeine-containing sodas, colas and chocolate, etc.) and alcohol starting 2 days prior to each period until the end of each blood collection period (72 hours post-dose). Subjects were prohibited from taking any prescription medication or any over-the-counter medication within 14 days prior to study start and throughout the study.

Dose and Treatment:
A. Test product:
2 x 100 mg Cyclosporine Capsules manufactured by Eon Labs Manufacturing, Inc., lot #711243, lot size capsules, potency 102.0%, content uniformity 101.3% (%CV=0.8), following an overnight fast.
B. Reference product:
2 x 100 mg Neoral[R] Capsules manufactured by Novartis, lot #23236, Exp. 4/1999, potency 100.1%, following an overnight fast.

Food and fluid intake: Subjects were required to fast from overnight prior to until 4 hours after drug administration. Water was prohibited for two hours before and two hours after dosing, but was allowed at all other times. Standard meals were served during the study.

Washout period: Two weeks

Blood samples: Blood samples were collected at 0 (pre-dose) and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2, 2.50, 3, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.0, 12.0 , 16.0 , 24.0 , 36.0, 48.0 and 72.0 hours post-dose.

Analytical Methodology

Analysis of cyclosporine was performed by the analytical division of . using the analytical method

Blood". The analytical method was developed and validated at

Sensitivity: The limit of quantitation was 5 ng/mL for cyclosporine

Linearity: The assay was linear over the concentration range of 5 to 1200 ng/mL.

Assay specificity: Blank human EDTA whole blood samples were carried through the described extraction procedure and chromatographed to determine the the extent to which endogenous whole blood components may contribute to chromatographic interference with the analyte or the internal standard. No significant interference was observed in 8 drug free EDTA whole blood samples.

Recovery: The mean recovery values for cyclosporine in human whole blood were 72.3%, 68.5% and 75.4% at concentrations of 15.0, 701.0 and 1400.0 ng/mL, respectively.

Interday precision: Interday precision for quality control samples ranged from 5.6% to 8.7% for cyclosporine.

Stability: Long term stability: Cyclosporine was stable for a period of 193 days in human whole blood at -20°C.
Freeze-Thaw: Cyclosporine was stable after three freeze-thaw cycles in human whole blood at -20°C.

Statistical Analysis:

Statistical analysis was performed on cyclosporine data using SAS. Analysis of variance was performed using the GLM procedure. Pharmacokinetics parameters were evaluated for treatment, sequence and period effects. The two one-sided tests were used to estimate the 90% confidence interval. The subjects in the study were dosed in two separate groups. An analysis of variance was performed to assess the group effect and determine the poolability of the two groups. A mode with terms for groups, sequences, group by sequence interaction, subjects within the group by sequence interaction, period within group interaction, treatments and treatment by group interaction was performed. No statistically significant group effects were observed for the pharmacokinetics parameters by using the above model.

IV. In Vivo Results:

Thirty-six volunteers and 2 alternates were initially enrolled in the study. Of the 38 subjects only 31 subjects were actually enrolled in the study and assigned a randomized number. Subject Nos. 15 and 18 dropped out prior to Period 2 for personal reasons and 35 dropped out after the 24.0 hour post-dose blood collection in Period 1. Twenty-nine (29) subjects completed the study. It was therefore decided to enroll 7 additional subjects in order to end up with 36 evaluable subjects. Only 6 of these subjects completed the study, giving a total of 35 subjects. Statistical analysis was initially performed in all 35 subjects who completed the study. Subject #36 experienced abdominal cramps, nausea and vomiting during the second period (test formulation). These symptoms started 10 hours post-dose. However, blood concentrations during the second period were substantially lowered, compared to the first period, for that subject. The firm speculated that these gastro-intestinal problems could have reduced blood and bile flow to the GI tract, they may also have reduced cyclosporine absorption during the second period for that subject. Therefore, the firm removed this subject from the final statistical analysis. Thirty-six adverse events were reported in eighteen of the thirty-eight subjects enrolled in the study. None of the adverse events resulted in dropping any subject from the study, nor they were considered serious (all adverse events are summarized in Table C3, Vol 1.3, page 02122).

The blood concentrations and pharmacokinetic parameters for cyclosporine are summarized in Table I.

Table I

Mean Blood Cyclosporine Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 200 mg (2x100 mg Capsules) Under Fasting Conditions

(N=34)

Time hr	Eon Test Product Lot #711243 ng/mL (CV)	Novartis Reference Product Lot #23236 ng/mL (CV)
0	0	0
0.25	8.28(171.0)	6.88(203.8)
0.50	194.97(88.1)	185.16(75.1)
0.75	479.47(51.5)	529.94(52.8)
1.00	689.70(32.9)	787.98(40.1)
1.25	789.40(23.7)	904.10(28.1)
1.50	778.62(19.2)	885.29(23.8)
1.75	736.06(18.5)	824.64(23.1)
2	663.99(17.6)	747.60(23.3)
2.50	549.83(21.3)	604.30(23.3)
3	442.51(23.4)	479.70(24.6)
3.5	364.79(24.3)	391.11(26.9)
4	301.31(22.3)	314.46(26.9)
4.5	257.69(22.5)	270.03(24.2)
5.0	218.29(21.6)	232.29(25.4)
6.0	164.51(22.5)	181.37(24.0)
8.0	114.87(21.5)	126.25(23.8)
10.0	79.21(20.5)	84.02(24.9)
12.0	57.50(21.1)	61.32(26.1)
16.0	35.08(21.7)	38.21(25.6)
24.0	18.89(23.3)	20.35(28.0)
36.0	7.81(36.8)	8.71(40.2)
48.0	4.20(82.7)	4.88(83.4)
72.0	0.59(335.7)	0.92(255.0)

			T/R	90% CI
AUC(0-t) (ng.hr/mL)	3610.6(18)	3966.3(23)	0.91	
AUCinf (ng.hr/mL)	3715.1(19)	4085.3(23)	0.91	
Cmax (ng/mL)	859.2(17)	983.8(24)	0.87	
Tmax (hr)	1.52	1.40		
Kel (1/hr)	0.066	0.063		
Half-Life (hr)	12.04	13.13		

LnAUC(0-t)	86.7-94.8%
LnAUCinf	86.5-94.2%
LnCmax	81.4-91.4%

1. The mean cyclosporine blood levels peaked at 1.25 hours for both the test and the reference products following their administration under fasting conditions.

2. For Eon's cyclosporine, the mean AUC(0-t), AUCinf and Cmax values were 9.0%, 9.1% and 12.7% lower, respectively, than those for the reference product values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUC(0-t), AUCinf and Cmax.

3. Additional analysis of variance was performed by the reviewer. After including subject #36 in the statistical analysis and employing the following model

Y = GRP SEQ SUBJ(SEQ*GRP) PER(GRP) TRT;

The following 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax were obtained:

Cyclosporine

LnAUC(0-t)	84.3-96.5%
LnAUCinf	84.5-96.1%
LnCmax	80.0-94.4%

The 90% confidence intervals for the above pharmacokinetics parameters calculated using the above model remained within the acceptable range of 80-125%.

V. Study #ANA-97-133 for Single-Dose, 3-way Crossover Study of Cyclosporine Capsules, 100 mg, Under Fasting and Nonfasting Conditions:

The objectives of this study were to compare the rate and extent of absorption of a test and a reference cyclosporine 100 mg soft gelatin capsule (test cyclosporine 100 mg soft gelatin capsule by Eon Labs Manufacturing Inc., USA versus Sandoz Pharmaceuticals Corporation USA (New name Novartis) Neoral®) administered as 2 x 100 mg soft gelatin capsules under non-fasting conditions, and to compare the rate and extent of absorption of a test cyclosporine 100 mg soft gelatin capsule by Eon Labs Manufacturing Inc., USA under fasting and non-fasting conditions.

Sponsor: Eon Labs Manufacturing, Inc.

Laurelton, New York

Study site:

Study design: Open-label, randomized, 3-way crossover, six-sequence study under fasting and nonfasting conditions.

Dosing dates: February 6, 1998, Period I
February 20, 1998, Period II
March 6, 1998, Period III

Analytical Date: From March 10 to March 25, 1998

Subjects: A total of 18 healthy non-smoking, Caucasian males and 6 alternates were enrolled and 22 subjects completed the study. Subject Nos. 06 and 15 dropped out prior to Period 2 for personal reasons. According to the protocol, data from the first 18 subjects to complete the study was to be analyzed. All subjects met the inclusion and exclusion criteria described in the protocol and were judged to be medically healthy based on medical history, medication history, physical examination, ECG, urine drug screen, urinalysis and clinical laboratory tests, including HIV antibody, hepatitis B (HB_sAg) and C (HCV). Their ages ranged from 19 to 45 and their weights did not deviate by more than 15% from their ideal body weights, based on the 1983 Metropolitan height and weight tables. Screening procedures took place within 28 days prior to Period 1.

Dose and treatment: A. 2 x 100 mg Cyclosporine Capsules, lot #711243, manufactured by Eon Labs Manufacturing, Inc., following a standard breakfast.

B. 2 x 100 mg Neoral^R Capsules, lot #23236 manufactured by Novartis, following a standard breakfast.

C. 2 x 100 mg Cyclosporine Capsules, lot #711243, manufactured by Eon Labs Manufacturing, Inc., under fasting conditions.

Food and fluid intake: Subjects on regimens A and B were required to fast overnight until 30 minutes prior to their scheduled dosing times, when they were administered breakfast (1 fried egg, 1 serving of hashed browned potatoes, 1 slice of bacon, 1 buttered English muffin, 1 slice of cheese, 8 ounces of whole milk and 6 ounces of orange juice). Subjects on regimen C were required to fast overnight for 10 hours before dosing and for 4 hours thereafter. Water was not permitted from two hours before dosing until two hours thereafter, but was allowed at all other times.

Washout period: Two weeks

Blood samples: Same as the fasting study.

Analytical Methodology

Same as the study above.

Data Analysis

ANOVA was performed with subjects within sequence, period, drug (i.e. formulations), and sequence as factors for AUC(0-t), AUCinf, Cmax and Tmax. Area under the curve was determined using linear trapezoidal method.

VI. In Vivo Results:

Eighteen (18) volunteers and 6 alternates were enrolled in the study. According to the protocol, data from the first 18 subjects to complete the study was to be analyzed. However, it was decided to break the randomization code before the completion of the analytical portion in order to replace subjects #6 and #15 (drop-outs) by subjects #20 and #21. Thus, all statistical analyses were carried out with 18 subjects. Forty-eight adverse events were reported in eighteen of the twenty-four subjects enrolled in the study. None of the adverse events resulted in dropping any subject from the study, nor they were considered serious (all adverse events are summarized in Table C3, Vol 1.8, page 04303).

The blood concentrations and pharmacokinetic parameters for cyclosporine are summarized in Table II.

Table II

Mean Blood Cyclosporine Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 200 mg(2x100 mg Capsules) Cyclosporine Under Fasting and Nonfasting Conditions

(N=18)

Time	Treatment A Eon Lot #711243 Nonfasting	Treatment B Novartis Lot #23236 Nonfasting	Treatment C Eon Lot #711243 Fasting
hr	ng/mL (C.V.)	ng/mL (C.V.)	ng/mL (C.V.)
0	0.00	0.00	0.00
0.25	4.36 (235.5)	8.01 (171.5)	20.72 (138.2)
0.50	198.12 (117.4)	274.78 (82.2)	266.40 (58.4)
0.75	536.85 (74.1)	651.17 (65.9)	608.73 (34.8)
1.00	783.54 (53.8)	831.87 (57.3)	825.45 (24.5)
1.25	925.53 (41.4)	875.79 (47.0)	869.48 (16.7)
1.50	925.15 (31.2)	849.59 (38.2)	845.74 (19.4)
1.75	870.61 (25.6)	801.04 (26.5)	769.59 (17.2)
2.00	822.25 (23.2)	738.62 (21.4)	690.24 (18.4)
2.5	670.72 (20.1)	618.51 (19.5)	540.54 (19.0)
3	535.13 (22.0)	509.27 (20.1)	430.73 (22.1)
3.5	449.70 (23.1)	425.39 (22.8)	362.25 (21.8)
4	378.82 (26.1)	349.91 (22.4)	297.75 (22.2)
4.5	334.24 (28.3)	310.29 (21.2)	267.33 (22.6)
5	276.69 (25.7)	284.03 (22.3)	228.08 (22.1)
6	210.33 (25.3)	210.63 (20.3)	189.30 (22.4)
8	137.23 (22.4)	135.79 (22.2)	128.94 (22.7)
10	95.79 (26.3)	93.69 (22.5)	87.03 (27.2)
12	67.77 (24.3)	68.60 (23.7)	61.59 (26.7)
16	43.03 (26.1)	42.13 (25.5)	37.70 (25.3)
24	22.70 (30.3)	21.95 (28.6)	19.18 (28.8)
36	10.62 (27.5)	9.76 (31.0)	9.53 (28.2)
48	6.74 (48.2)	6.35 (52.8)	5.57 (50.9)
72	1.71 (168.5)	0.85 (293.4)	1.28 (196.6)
AUC(0-t) (ng.hr/mL)	4442.9 (22)	4294.8 (23)	3924.8 (19)
AUCinf (ng.hr/mL)	4578.6 (22)	4414.7 (23)	4040.0 (18)
Cmax(ng/mL)	1039.7 (26)	1014.4 (29)	924.9 (16)
Tmax(hr)	1.54	1.40	1.25
T1/2 (hr)	16.07	13.26	14.82
Kel (1/hr)	0.05	0.06	0.05

	A/B Arithmetic Mean	A/B Geometric Mean
AUC(0-t)	1.03	1.03
AUCinf	1.04	1.04
Cmax	1.02	1.02

1. The Cyclosporine blood levels peaked at 1.25 hours for both the test and the reference products under nonfasting conditions and for the test product under fasting conditions.

2. For Eon's test product, the mean AUC(0-t), AUCinf and Cmax values were 3.4%, 3.7% and 2.5% higher, respectively, than the reference product values under nonfasting conditions. The ratios of the arithmetic and geometric means for Cyclosporine are within the acceptable range of 0.8-1.2 and 0.8-1.25, respectively, under nonfasting conditions for the above parameters.

3. For the test product, the mean AUC(0-t) and Cmax values after dosing with food increased by 13.2% and 12.4%, respectively, compared to the values reported in the fasting state.

VII. Formulation:

Eon's formulation for its Cyclosporine Soft Gelatin Capsules, 100 mg is shown below:

Component	Mg/Capsules
Cyclosporine,	100.0
alcohol,	
d-a Tocopheryl polyethylene glycol 1000 succinate	
Polyethylene glycol 400,	
Polyoxyl 40 hydrogenated Castor oil	
Purified water,	
Gelatin,	
Sorbitol	
Total	

IIIV. In Vitro Disintegration Testing: (USP method)

The firm has submitted disintegration results for its Cyclosporine, 100 mg Soft Gelatin Capsules, the results are shown in Table III. The disintegration testing for the test and reference products is summarized below:

Method:	USP 23 Disintegration Apparatus without Disk
Frequency:	30 Cycles per minutes
Medium:	1000 mL of water at 37°c
Number of Capsules:	12
Test product:	Eon's Cyclosporine Capsules, 100 mg, lot #711243
Reference product:	Novartis' Neoral[R] Capsules, 100 mg, lot #23236
Specification:	

Disintegration testing results are shown in Table III.

IX. In Vitro Dissolution Testing: (Pharmacopeial Forum, May-June 1998, Volume 24, Number 3, page 6155, method A)

The firm has submitted dissolution results for its Cyclosporine, 100 mg Soft Gelatin Capsules, the results are shown in Table IV. The dissolution testing for the test and reference products is summarized below:

Method:	USP apparatus II at 75 rpm
Medium:	1000 mL of 0.1N HCl containing 4 mg/mL of Lauryldimethylamine-N-Oxide
Number of Capsules:	12
Test product:	Eon's Cyclosporine Capsules, 100 mg, lot #711243
Reference product:	Novartis' Neoral[R] Capsules, 100 mg, lot #23236

Specification:

Dissolution testing results are shown in Table IV.

X. Comments:

1. The firm's in vivo bioequivalence studies under fasting and nonfasting conditions are acceptable. The test product is similar in both rate and extent of absorption to the reference product. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% under fasting conditions for

Cyclosporine. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf and Cmax under nonfasting conditions.

2. The in vitro dissolution testing submitted by the firm on its Cyclosporine, 100 mg Soft Gelatin Capsules, is acceptable

XI. Recommendations:

1. The single-dose bioequivalence study #ANA-97-132 under fasting conditions, conducted by Eon Labs Manufacturing, Inc., on its Cyclosporine 100 mg Soft Gelatin Capsule, lot #711243, comparing it to Neoral[R] 100 mg Soft Gelatin Capsule, manufactured by Novartis, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Eon's Cyclosporine Soft Gelatin Capsule, 100 mg is bioequivalent to the reference product, Neoral[R] Soft Gelatin Capsule, 100 mg, manufactured by Novartis under fasting conditions.

2. The single-dose post-prandial bioequivalence study #ANA-97-133, conducted by Eon Labs Manufacturing, Inc., on its Cyclosporine 100 mg Soft Gelatin Capsule, comparing it to Neoral[R] 100 mg Soft Gelatin Capsule, manufactured by Novartis, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Eon's Cyclosporine Soft Gelatin Capsule, 100 mg is bioequivalent to the reference product, Neoral[R] Soft Gelatin Capsule, 100 mg, manufactured by Novartis under nonfasting conditions.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of 0.1N HCl containing 4 mg/mL of Lauryldimethylamine-N-Oxide at 37°C using USP 23 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

> Not less than [redacted] (Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

The firm should be informed of the above recommendations.

Moneb H. /S/ akary, Ph.D. Date: 11/13/98
Review Branch III
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

AADA: 65-017 APPLICANT: Eon Labs Manufacturing, Inc.

DRUG PRODUCT: Cyclosporine Soft Gelatin Capsules, USP 100 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in Pharmacopeial Forum, May-June 1998, Volume 24, Number 3, page 6155, method A.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

1-198

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT

/S/ _____ Date: 11/13/98

/S/

Concur: _____ Date: 11/17/98

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Cyclosporine
100 mg Soft Gelatin Capsules
AADA #65-017
Reviewer: Moheb H. Makary
WP 65017sd.698

Eon Labs Manufacturing, Inc.
Laurelton, New York
Submission Date:
June 8, 1998
September 11, 1998

Review of In-Vivo Bioequivalence Studies

I. Objective:

The firm submitted two bioequivalence studies to assess the bioequivalence of Eon's Cyclosporine Soft Gelatin Capsules, 100 mg, to Novartis' Neoral^{R} 100 mg Capsule (microemulsion). Disintegration testing for Eon's Cyclosporine 100 mg capsules and Neoral^{R} 100 mg capsules and the composition for the Cyclosporine 100 mg capsules were also submitted.

II. BACKGROUND:

Cyclosporine (cyclosporin A) is a potent immunosuppressive antibiotic indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. It is also indicated for treatment of chronic rejection in patients previously treated with other immunosuppressive agents. The immunosuppressive action of cyclosporine appears mainly to involve inhibition of lymphocytic proliferation and function.

Following oral administration, absorption of cyclosporine from the gastrointestinal tract is variable and incomplete. The time to peak blood cyclosporine concentrations (Tmax) ranged from 1.5 to 2.0 hours in renal transplant patients. The administration of food with cyclosporine decreased the area under the curve (AUC) and peak drug blood concentration (Cmax). A high-fat meal consumed 30 minutes before cyclosporine administration decreased the AUC by 13% and the Cmax by 33%. The effects of a low-fat meal were similar.

Cyclosporine is distributed largely outside the blood volume. In blood, the distribution is concentration-dependent, with approximately 33-47% in plasma, 4-9% in lymphocytes, 5-12% in granulocytes, and 41-58% in erythrocytes. At high concentrations, the binding capacity of leukocytes and erythrocytes becomes saturated. In plasma, approximately 90% is bound to proteins, primarily lipoproteins.

The disposition of cyclosporine from blood is generally biphasic, with a terminal half-life of approximately 8.4 hours (range 5 to 18 hours). Elimination is primarily biliary with only 6% of the dose (parent drug and metabolites) excreted in the urine. Cyclosporine is extensively metabolized but there is no major metabolic pathway. The role of metabolites in immunosuppression has not been established.

Cyclosporine capsules products are marketed by Novartis as Sandimmune® capsules, 25, 50 and 100 mg and Neoral® soft gelatin capsules (cyclosporine capsules for microemulsion), 25, 50 and 100 mg. Because the bioavailability of Neoral® is greater than that of Sandimmune®, the products are not bioequivalent and cannot be used interchangeably without physician supervision.

III. Study #ANA-97-132 for Single-Dose, two-way Crossover Study of Cyclosporine Capsule, 100 mg, Under Fasting Conditions

The objective of this study was to compare the rate and extent of absorption of a test and a reference cyclosporine 100 mg soft gelatin capsule (test cyclosporine 100 mg soft gelatin capsule versus Sandoz Pharmaceuticals Corporation USA (New name Novartis) Neoral®) administered as 2 x 100 mg soft gelatin capsules.

Sponsor: Eon Labs Manufacturing, Inc.
Laurelton, New York

Study site:

Study design: Open-label, single-dose, fasted, randomized, two-period crossover.

Dosing date: The study was conducted in two groups.
Group 1(subject Nos. 1-32, except 20),
Period I December 15, 1997
Period II January 4, 1998
Group II (subject Nos. 20, 33-38)
Period I January 4, 1998
Period II January 18, 1998

Analytical Date: Samples were analyzed from January 22 to March 13, 1998.

Subjects eligibility: A total of 38 healthy non-smoking, Caucasian males were enrolled and 35 subjects completed the study. Subject Nos. 15 and 18 dropped out prior to Period

2 for personal reasons and 35 dropped out after the 24.0 hour post-dose blood collection in Period 1. All subjects met the inclusion and exclusion criteria described in the protocol and were judged to be medically
healthy based on medical history, medication history, physical examination, ECG, urine drug screen, urinalysis and clinical laboratory tests, including HIV antibody, hepatitis B (HB_sAg) and C (HCV). Their ages ranged from 18 to 43 and their weights did not deviate by more than 15% from their ideal body weights, based on the 1983 Metropolitan height and weight tables. Screening procedures took place within 28 days prior to Period 1.
The study was conducted in two groups. Period 1 of ANA-97-132 (Subject Nos. 01-32, except 20) began on December 21, 1997 while Period 1 of ANA-97-132 (Subject Nos. 20, 33-38) began on January 04, 1998.

Restrictions: Subjects were instructed to abstain from food or drinks containing caffeine and/or xanthine (i.e. coffee, tea, caffeine-containing sodas, colas and chocolate, etc.) and alcohol starting 2 days prior to each period until the end of each blood collection period (72 hours post-dose). Subjects were prohibited from taking any prescription medication or any over-the-counter medication within 14 days prior to study start and throughout the study.

Dose and Treatment:
A. Test product:
2 x 100 mg Cyclosporine Capsules manufactured by Eon Labs Manufacturing, Inc., lot #711243, lot size capsules, potency 102.0%, content uniformity (not reported), following an overnight fast.
B. Reference product:
2 x 100 mg Neoral^R Capsules manufactured by Novartis, lot #23236, Exp. 4/1999, potency 100.1%, content uniformity (not reported), following an overnight fast.

Food and fluid intake: Subjects were required to fast from overnight prior to until 4 hours after drug administration. Water was prohibited for two hours before and two hours after dosing, but was allowed at all other

times. Standard meals were served during the study.

Washout period: Two weeks

Blood samples: Blood samples were collected at 0 (pre-dose) and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2, 2.50, 3, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.0, 12.0 , 16.0 , 24.0 , 36.0, 48.0 and 72.0 hours post-dose.

Analytical Methodology

Analysis of cyclosporine was performed by the analytical division of . using the analytical method

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Sensitivity: The limit of quantitation was 5 ng/mL for cyclosporine

Linearity: The assay was linear over the concentration range of 5 to 1200 ng/mL.

Assay specificity: Blank human EDTA whole blood samples were carried through the described extraction procedure and chromatographed to determine the the extent to which endogenous whole blood components may contribute to chromatographic interference with the analyte or the internal standard. No significant interference was observed in 8 drug free EDTA whole blood samples.

Recovery: The mean recovery values for cyclosporine in human whole blood were 72.3%, 68.5% and 75.4% at concentrations of 15.0, 701.0 and 1400.0 ng/mL, respectively.

Interday precision: Interday precision for quality control samples ranged from 5.6% to 8.7% for cyclosporine.

Stability: Long term stability: Cyclosporine was stable for a period of 193 days in human whole blood at -20°C.
Freeze-Thaw: Cyclosporine was stable after

three freeze-thaw cycles in human whole blood at -20°C.

Statistical Analysis:

Statistical analysis was performed on cyclosporine data using SAS. Analysis of variance was performed using the GLM procedure. Pharmacokinetics parameters were evaluated for treatment, sequence and period effects. The two one-sided tests were used to estimate the 90% confidence interval. The subjects in the study were dosed in two separate groups. An analysis of variance was performed to assess the group effect and determine the poolability of the two groups. A mode with terms for groups, sequences, group by sequence interaction, subjects within the group by sequence interaction, period within group interaction, treatments and treatment by group interaction was performed. No statistically significant group effects were observed for the pharmacokinetics parameters by using the above model.

IV. In Vivo Results:

Thirty-six volunteers and 2 alternates were initially enrolled in the study. Of these, 29 subjects completed the study. It was therefore decided to enroll 7 additional subjects in order to end up with 36 evaluable subjects. Only 6 of these subjects completed the study, giving a total of 35 subjects. Statistical analysis was initially performed in all 35 subjects who completed the study. Subject #36 experienced abdominal cramps, nausea and vomiting during the second period (test formulation). These symptoms started 10 hours post-dose. However, blood concentrations during the second period were substantially lowered, compared to the first period, for that subject. The firm speculated that these gastro-intestinal problems could have reduced blood and bile flow to the GI tract, they may also have reduced cyclosporine absorption during the second period for that subject. Therefore, the firm removed this subject from the final statistical analysis. Thirty-six adverse events were reported in eighteen of the thirty-eight subjects enrolled in the study. None of the adverse events resulted in dropping any subject from the study, nor they were considered serious (all adverse events are summarized in Table C3, Vol 1.3, page 02122).

The blood concentrations and pharmacokinetic parameters for cyclosporine are summarized in Table I.

Table I

Mean Blood Cyclosporine Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 200 mg (2x100 mg Capsules) Under Fasting Conditions

(N=34)

Time hr	Eon Test Product Lot #711243 ng/mL (CV)	Novartis Reference Product Lot #23236 ng/mL (CV)
0	0	0
0.25	8.28(171.0)	6.88(203.8)
0.50	194.97(88.1)	185.16(75.1)
0.75	479.47(51.5)	529.94(52.8)
1.00	689.70(32.9)	787.98(40.1)
1.25	789.40(23.7)	904.10(28.1)
1.50	778.62(19.2)	885.29(23.8)
1.75	736.06(18.5)	824.64(23.1)
2	663.99(17.6)	747.60(23.3)
2.50	549.83(21.3)	604.30(23.3)
3	442.51(23.4)	479.70(24.6)
3.5	364.79(24.3)	391.11(26.9)
4	301.31(22.3)	314.46(26.9)
4.5	257.69(22.5)	270.03(24.2)
5.0	218.29(21.6)	232.29(25.4)
6.0	164.51(22.5)	181.37(24.0)
8.0	114.87(21.5)	126.25(23.8)
10.0	79.21(20.5)	84.02(24.9)
12.0	57.50(21.1)	61.32(26.1)
16.0	35.08(21.7)	38.21(25.6)
24.0	18.89(23.3)	20.35(28.0)
36.0	7.81(36.8)	8.71(40.2)
48.0	4.20(82.7)	4.88(83.4)
72.0	0.59(335.7)	0.92(255.0)

			T/R	90% CI
AUC(0-t) (ng.hr/mL)	3610.6(18)	3966.3(23)	0.91	
AUCinf(ng.hr/mL)	3715.1(19)	4085.3(23)	0.91	
Cmax (ng/mL)	859.2(17)	983.8(24)	0.87	
Tmax (hr)	1.52	1.40		
Kel (1/hr)	0.066	0.063		
Half-Life(hr)	12.04	13.13		

LnAUC(0-t)	86.7-94.8%
LnAUCinf	86.5-94.2%
LnCmax	81.4-91.4%

1. The mean cyclosporine blood levels peaked at 1.25 hours for both the test and the reference products following their administration under fasting conditions.

2. For Eon's cyclosporine, the mean AUC(0-t), AUCinf and Cmax values were 9.0%, 9.1% and 12.7% lower, respectively, than those for the reference product values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUC(0-t), AUCinf and Cmax.

3. Additional analysis of variance was performed by the reviewer. After including subject #36 in the statistical analysis and employing the following model

Y = GRP SEQ SUBJ(SEQ*GRP) PER(GRP) TRT;

The following 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax were obtained:

Cyclosporine

LnAUC(0-t)	84.3-96.5%
LnAUCinf	84.5-96.1%
LnCmax	80.0-94.4%

The 90% confidence intervals for the above pharmacokinetics parameters calculated using the above model remained within the acceptable range of 80-125%.

V. Study #ANA-97-133 for Single-Dose, 3-way Crossover Study of Cyclosporine Capsules, 100 mg, Under Fasting and Nonfasting Conditions:

The objectives of this study were to compare the rate and extent of absorption of a test and a reference cyclosporine 100 mg soft gelatin capsule (test cyclosporine 100 mg soft gelatin capsule by Eon Labs Manufacturing Inc., USA versus Sandoz Pharmaceuticals Corporation USA (New name Novartis) Neoral®) administered as 2 x 100 mg soft gelatin capsules under non-fasting conditions, and to compare the rate and extent of absorption of a test cyclosporine 100 mg soft gelatin capsule by Eon Labs Manufacturing Inc., USA under fasting and non-fasting conditions.

Sponsor: Eon Labs Manufacturing, Inc.

Laurelton, New York

Study site:

Study design: Open-label, randomized, 3-way crossover, six-sequence study under fasting and nonfasting conditions.

Dosing dates: February 6, 1998, Period I
February 20, 1998, Period II
March 6, 1998, Period III

Analytical Date: From March 10 to March 25, 1998

Subjects: A total of 18 healthy non-smoking, Caucasian males and 6 alternates were enrolled and 22 subjects completed the study. Subject Nos. 06 and 15 dropped out prior to Period 2 for personal reasons. According to the protocol, data from the first 18 subjects to complete the study was to be analyzed. All subjects met the inclusion and exclusion criteria described in the protocol and were judged to be medically healthy based on medical history, medication history, physical examination, ECG, urine drug screen, urinalysis and clinical laboratory tests, including HIV antibody, hepatitis B (HB_sAg) and C (HCV). Their ages ranged from 19 to 45 and their weights did not deviate by more than 15% from their ideal body weights, based on the 1983 Metropolitan height and weight tables. Screening procedures took place within 28 days prior to Period 1.

Dose and treatment: A. 2 x 100 mg Cyclosporine Capsules, lot #711243, manufactured by Eon Labs Manufacturing, Inc., following a standard breakfast.

B. 2 x 100 mg Neoral^R Capsules, lot #23236 manufactured by Novartis, following a standard breakfast.

C. 2 x 100 mg Cyclosporine Capsules, lot #711243, manufactured by Eon Labs Manufacturing, Inc., under fasting conditions.

Food and fluid intake: Subjects on regimens A and B were required to fast overnight until 30 minutes prior to their scheduled dosing times, when they were administered breakfast (1 fried egg, 1 serving of hashed browned potatoes, 1 slice of bacon, 1 buttered English muffin, 1 slice of cheese, 8 ounces of whole milk and 6 ounces of orange juice). Subjects on regimen C were required to fast overnight for 10 hours before dosing and for 4 hours thereafter. Water was not permitted from two hours before dosing until two hours thereafter, but was allowed at all other times.

Washout period: Two weeks

Blood samples: Same as the fasting study.

Analytical Methodology

Same as the study above.

Data Analysis

ANOVA was performed with subjects within sequence, period, drug (i.e. formulations), and sequence as factors for AUC(0-t), AUCinf, Cmax and Tmax. Area under the curve was determined using linear trapezoidal method.

VI. In Vivo Results:

Eighteen (18) volunteers and 6 alternates were enrolled in the study. According to the protocol, data from the first 18 subjects to complete the study was to be analyzed. However, it was decided to break the randomization code before the completion of the analytical portion in order to replace subjects #6 and #15 (drop-outs) by subjects #20 and #21. Thus, all statistical analyses were carried out with 18 subjects. Forty-eight adverse events were reported in eighteen of the twenty-four subjects enrolled in the study. None of the adverse events resulted in dropping any subject from the study, nor they were considered serious (all adverse events are summarized in Table C3, Vol 1.8, page 04303).

The blood concentrations and pharmacokinetic parameters for cyclosporine are summarized in Table II.

Table II

Mean Blood Cyclosporine Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 200 mg(2x100 mg Capsules) Cyclosporine Under Fasting and Nonfasting Conditions

(N=18)

Time	Treatment A Eon Lot #711243 Nonfasting	Treatment B Novartis Lot #23236 Nonfasting	Treatment C Eon Lot #711243 Fasting
hr	ng/mL (C.V.)	ng/mL (C.V.)	ng/mL (C.V.)
0	0.00	0.00	0.00
0.25	4.36 (235.5)	8.01 (171.5)	20.72 (138.2)
0.50	198.12 (117.4)	274.78 (82.2)	266.40 (58.4)
0.75	536.85 (74.1)	651.17 (65.9)	608.73 (34.8)
1.00	783.54 (53.8)	831.87 (57.3)	825.45 (24.5)
1.25	925.53 (41.4)	875.79 (47.0)	869.48 (16.7)
1.50	925.15 (31.2)	849.59 (38.2)	845.74 (19.4)
1.75	870.61 (25.6)	801.04 (26.5)	769.59 (17.2)
2.00	822.25 (23.2)	738.62 (21.4)	690.24 (18.4)
2.5	670.72 (20.1)	618.51 (19.5)	540.54 (19.0)
3	535.13 (22.0)	509.27 (20.1)	430.73 (22.1)
3.5	449.70 (23.1)	425.39 (22.8)	362.25 (21.8)
4	378.82 (26.1)	349.91 (22.4)	297.75 (22.2)
4.5	334.24 (28.3)	310.29 (21.2)	267.33 (22.6)
5	276.69 (25.7)	284.03 (22.3)	228.08 (22.1)
6	210.33 (25.3)	210.63 (20.3)	189.30 (22.4)
8	137.23 (22.4)	135.79 (22.2)	128.94 (22.7)
10	95.79 (26.3)	93.69 (22.5)	87.03 (27.2)
12	67.77 (24.3)	68.60 (23.7)	61.59 (26.7)
16	43.03 (26.1)	42.13 (25.5)	37.70 (25.3)
24	22.70 (30.3)	21.95 (28.6)	19.18 (28.8)
36	10.62 (27.5)	9.76 (31.0)	9.53 (28.2)
48	6.74 (48.2)	6.35 (52.8)	5.57 (50.9)
72	1.71 (168.5)	0.85 (293.4)	1.28 (196.6)
AUC(0-t) (ng.hr/mL)	4442.9 (22)	4294.8 (23)	3924.8 (19)
AUCinf (ng.hr/mL)	4578.6 (22)	4414.7 (23)	4040.0 (18)
Cmax(ng/mL)	1039.7 (26)	1014.4 (29)	924.9 (16)
Tmax(hr)	1.54	1.40	1.25
T1/2 (hr)	16.07	13.26	14.82
Kel (1/hr)	0.05	0.06	0.05

	A/B Arithmetic Mean	A/B Geometric Mean
AUC(0-t)	1.03	1.03
AUCinf	1.04	1.04
Cmax	1.02	1.02

1. The Cyclosporine blood levels peaked at 1.25 hours for both the test and the reference products under nonfasting conditions and for the test product under fasting conditions.

2. For Eon's test product, the mean AUC(0-t), AUCinf and Cmax values were 3.4%, 3.7% and 2.5% higher, respectively, than the reference product values under nonfasting conditions. The ratios of the arithmetic and geometric means for Cyclosporine are within the acceptable range of 0.8-1.2 and 0.8-1.25, respectively, under nonfasting conditions for the above parameters.

3. For the test product, the mean AUC(0-t) and Cmax values after dosing with food increased by 13.2% and 12.4%, respectively, compared to the values reported in the fasting state.

VII. Formulation:

Eon's formulation for its Cyclosporine Soft Gelatin Capsules, 100 mg is shown below:

Component	Mg/Capsules
Cyclosporine,	100.0
alcohol,	
d-a Tocopheryl polyethylene glycol succinate	
Polyethylene glycol 400,	
Polyoxyl 40 hydrogenated Castor oil	
Purified water,	
Gelatin,	
Sorbitol	
- :rol)	
Total	

IIIV. In Vitro Disintegration Testing: (USP method)

The firm has submitted disintegration results for its Cyclosporine, 100 mg Soft Gelatin Capsules, the results are shown in Table III. The disintegration testing for the test and reference products is summarized below:

Method:	USP 23 Disintegration Apparatus without Disk
Frequency:	30 Cycles per minutes
Medium:	1000 mL of water at 37°c
Number of Capsules:	12
Test product:	Eon's Cyclosporine Capsules, 100 mg, lot #711243
Reference product:	Novartis' Neoral[R] Capsules, 100 mg, lot #23236
Specification:	

Disintegration testing results are shown in Table III.

IX. Deficiency Comments:

1. In the Statistical Report No. ANA-97-132 (the single dose bioequivalence fasting study), it was stated that 36 subjects and 2 alternates were initially enrolled in the study. Of these, 29 subjects completed the study. Hence, an additional 7 subjects were enrolled and 6 subjects completed. In the Clinical Report No. ANA-97-132, it was stated that a total of 38 subjects were enrolled and 35 completed the study. Reasons were provided only for the withdrawal of subjects 15 and 18. The firm should provide the reasons for each of the 9 subjects who did not complete the study from the initial enrollment and the one subject from the second enrollment.

2. The firm should provide the content uniformity data for the test and the reference products.

3. The firm should submit dissolution testing data on its 100 mg soft gelatin capsules using the method published in Pharmacopeial Forum, May-June 1998, Volume 24, Number 3.

X. Recommendations:

1. The single-dose bioequivalence study #ANA-97-132 under fasting conditions, conducted by Eon Labs Manufacturing, Inc., on its Cyclosporine 100 mg Soft Gelatin Capsules, lot #711243, comparing it to Neoral[R] 100 mg Soft Gelatin Capsules, manufactured by Novartis, has been found incomplete by the Division of

Bioequivalence for the reasons given in deficiency comments 1 & 2.

2. The single-dose post-prandial bioequivalence study #ANA-97-133, conducted by Eon Labs Manufacturing, Inc., on its Cyclosporine 100 mg Soft Gelatin Capsules, comparing it to Neoral[R] 100 mg Soft Gelatin Capsules, manufactured by Novartis, has been found incomplete by the Division of Bioequivalence for the reason given in deficiency comment 2.

The firm should be informed of the deficiency comments and recommendations.

/S/

Moheb H. Makary, Ph.D.
Review Branch III
Division of Bioequivalence

Date: 9/23/98

RD INITIALLED BDAVIT and 9/23/98 /S/
FT INITIALLED BDAVIT

Date: 9/23/98

Concur: /S/

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Date: 10/9/98

on

BIOEQUIVALENCY DEFICIENCIES

AADA: 65-017 APPLICANT: Eon Labs Manufacturing, Inc.

DRUG PRODUCT: Cyclosporine Soft Gelatin Capsules, USP 100 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. In the Statistical Report No. ANA-97-132 (the single dose bioequivalence fasting study), it was stated that 36 subjects and 2 alternates were initially enrolled in the study. Of these, 29 subjects completed the study. Hence, an additional 7 subjects were enrolled and 6 subjects completed. In the Clinical Report No. ANA-97-132, it was stated that a total of 38 subjects were enrolled and 35 completed the study. Reasons were provided only for the withdrawal of subjects 15 and 18. Please clarify this discrepancy and provide the reasons for each of the 9 subjects who did not complete the study from the initial enrollment and the one subject from the second enrollment.

2. Please provide the content uniformity data for the test and the reference products.

3. Please submit comparative dissolution testing data on the Cyclosporine Soft Gelatin Capsules, USP 100 mg, using the method published in Pharmacopeial Forum, May-June 1998, Volume 24, Number 3.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY DEFICIENCIES

AADA: 65-017 APPLICANT: Eon Labs Manufacturing, Inc.

DRUG PRODUCT: Cyclosporine Soft Gelatin Capsules, USP 100 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. In the Statistical Report No. ANA-97-132 (the single dose bioequivalence fasting study), it was stated that 36 subjects and 2 alternates were initially enrolled in the study. Of these, 29 subjects completed the study. Hence, an additional 7 subjects were enrolled and 6 subjects completed. In the Clinical Report No. ANA-97-132, it was stated that a total of 38 subjects were enrolled and 35 completed the study. Reasons were provided only for the withdrawal of subjects 15 and 18. Please clarify this discrepancy and provide the reasons for each of the 9 subjects who did not complete the study from the initial enrollment and the one subject from the second enrollment.

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Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

8)

BIOEQUIVALENCY - DEFICIENCIES Submission Date: June 8, 1998
September 11, 1998

1. **FASTING STUDY** (STF) Strengths: 100 mg
   Clinical: **Outcome: IC**
   Analytical:

2. **FOOD STUDY** (STP) Strengths: 100 mg
   Clinical: **Outcome: IC**
   Analytical:

3. ~~**DISINTEGRATION DATA** (DIS)~~ ~~All Strengths~~
   ~~**Outcome: AC**~~

4. **STUDY AMENDMENT** (STA) 9/11/98 Strengths: 100 MG
   Outcome: AC

Outcome Decisions:

IC - Incomplete

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

September 11, 1998

Ms. Lizzie Sanchez, Pharm.D.
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA [illegible]

N/AB

Re: General Correspondance - Division of Bioequivalence
Cyclosporin Soft Gelatin Capsules, USP, 100 mg
ANDA 65-017

Dear Ms. Sanchez:

In regards to your request of September 8th, enclosed is a re-formatted diskette for the bioequivalence studies ANA-97-132 and ANA-97-133, in ASCII format. If any further information is required, do not hesitate to call me at (718) 276-8607 x330.

Sincerely,
Eon Labs Manufacturing, Inc.

Sadie Ciganek
Vice President Regulatory Affairs

RECEIVED

SEP 11 1998

GENERIC DRUGS

BIOAVAILABILITY

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120
718-276-8635

ORIG AMENDMENT
N/PE

November 12, 1998

Nasser Mahmud, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

-Telephone Bioequivalence Amendment -

Re: ANDA 65-017
Cyclospsorin Soft Gelatin Capsules, 100 mg USP
Two-way Single Dose Fasting Study, ANA 97-132, Conducted by ....

Dear Dr. Mahmud;

As a follow-up to your November 5th telephone call regarding the above referenced bioequivalence study for Cyclosporin Soft Gelatin Capsules, we are providing the following information:

Comment #1
Provide an explanation for the total number of subjects who were enrolled and completed the study.

Response

As indicated in Volume 5, Page No. 02112 of the original Abbreviated New Drug Application, a total number of thirty eight (38) subjects were enrolled in the Cyclosporin biostudy ANA-97-132. However of these, only thirty five (35) subjects completed the study with three drop outs. The thirty five subjects (35) were enrolled in two groups as described below:

Originally, thirty six (36) subjects plus two (2) alternates were recruited for the Cyclosporin biostudy. Only thirty one (31) subjects were actually enrolled in the study and assigned a randomization number. The other seven subjects did not show up on the day of dosing and were never entered into the study. Of the 31 subjects, Nos 15 and 18 elected to withdraw due to personal reasons and did not complete the study. Therefore, twenty nine (29) subjects completed the study as **group one**. An additional seven (7) subjects were subsequently enrolled to achieve the correct number of evaluable subjects needed to satisfy the clinical protocol requirements. Of

1998

the seven subjects, No 35 dropped out after period one dosing and did not return for period two. This left six (6) subjects completing the study as **group two**.

Reference to the recruitment and enrollment of the two groups can be found on pages 02013 and 02022 of the Abbreviated New Drug Application.

In summary, considering the overall enrollment and drop-outs between both groups one and two, a total of thirty eight (38) subjects were dosed while only thirty five subjects (n=35) completed the study and three (3) subjects dropped out. A more detailed discussion of the subject enrollment and dropouts has been provided by Anapharm in **ATTACHMENT 1.**

Comment #2
Provide content uniformity data by assay for bio/ANDA lot # 711243 and reference lot #23236.

Response

The official USP 23 monograph, page 444, does not require a content uniformity test for the Cyclosporin Soft Gelatin Capsules. However, supplement 7, page 3984, specifies that content uniformity by weight variation may apply for liquid filled capsules.

Content uniformity by assay is not required for cyclosporin capsules since the capsule fill is a homogeneous solution. The concentration and potency of the solution is absolute and will not change during the encapsulation process. The potency value determined on a QC sample of a solution applies to the overall uniform mixture. The critical parameter for determining uniformity of dose for a liquid filled capsule is to measure the amount of solution used to fill each capsule. The fill weight is directly proportional to the amount of active drug in the homogeneous solution. Based on this rationale, content uniformity by weight variation will be used as the criteria in our prospective validation studies for the production batches.

For information purposes only, content uniformity by assay was performed during the pre-validation studies for the subject bio/ANDA lot number 711243. A summary of that data is provided for your review, **ATTACHMENT 2**.

Comment #3
Request for comparative dissolution profiles between the test and reference drug according to the newly proposed dissolution method published in the

Pharm Forum, Volume 24, number 3.

Response

The official USP 23 monograph, supplement 9, page 3984, now provides for dissolution testing of Cyclosporin soft gelatin capsules for QC release. The supplement provides for a time limit specification of NMT thirty minutes for rupture of the capsule wall. No quantitative determination is required. New dissolution requirements were recently published in the Pharmacopeial Forum, Volume 24, Number 3, page 6155, proposing a quantitative specification of NLT 75% (Q) of the labeled amount is dissolved in 60 minutes.

In accordance with your request, Eon Labs performed dissolution profiles comparing the test and reference products according to the proposed Pharmacopeial Forum test method (**Method A**) and specifications. A copy of the **Dissolution Profile Report** summarizing the data is provided, **ATTACHMENT 3.** Although we were able to meet the dissolution criteria for cyclosporin soft gelatin capsules, Eon Labs feels that a quantitative dissolution test for QC release is not meaningful since the capsules are filled with a solution. The rate limiting and most critical parameter for this product is the rupture time. Once the capsule opens, the entire capsule content will diffuse and mix with the dissolution medium. The mixing of the active with the dissolution media is a physical property and depends on the partition coefficient of the active and the lipophilicity of the dissolution medium, not the capsule formulation.

It is Eon Labs intention to petition the Pharmacopeial Forum in the immediate future with our comments in this regard to eliminate quantitative dissolution requirements for cyclosporin soft gelatin capsules.

We hope the responses satisfactorily address your comments and that review of our application will proceed accordingly. If you have any other questions, do not hesitate to call me at (718) 276-8607 330.

Regards,
Eon Labs a Health Care Company

Sadie M. Ciganek
Vice President Regulatory Affairs

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

AADA: 65-017 APPLICANT: Eon Labs Manufacturing, Inc.

DRUG PRODUCT: Cyclosporine Soft Gelatin Capsules, USP 100 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in Pharmacopeial Forum, May-June 1998, Volume 24, Number 3, page 6155, method A.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA 65-017 APPLICANT: Eon Labs Manufacturing, Inc.

DRUG PRODUCT: Cyclosporine Capsules, 100 mg and 25 mg

...ision of Bioequivalence has completed its review and ...further questions at this time.

...nowledge that the following dissolution testing has ...ncorporated into your stability and quality control ...ams:

...issolution testing should be conducted in 500 mL of ... containing 2 mg/mL of Lauryldimethylamine-N-Oxide ...sing USP 23 apparatus II (paddle) at 75 rpm. The ...oduct should meet the following specifications:

... less than Q) of the labeled amount of the ...ug in the dosage form is dissolved in 60 minutes.

... note that the bioequivalency comments provided in ...communication are preliminary. These comments are ... to revision after review of the entire application, ...consideration of the chemistry, manufacturing and ...ls, microbiology, labeling, or other scientific or ...tory issues. Please be advised that these reviews ...sult in the need for additional bioequivalency ...ation and/or studies, or may result in a conclusion ...e proposed formulation is not approvable.

Sincerely yours,

/S/

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

HFD-

/S/

EQUIVALENCY - ACCEPTABLE submission d